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Schindler, Valeria ; Huellner, Martin ; Murray, Fritz ; Schnurre, Larissa ; Becker, Anton S ; Bordier, Valentine ; Pohl, Daniel

Abstract: Background/Aims Small intestinal bacterial overgrowth (SIBO) is a common condition in disorders of gut-brain interaction (DGBI). Recently, a combined scintigraphy-lactulose hydrogen breath test (ScLHBT) was described as an accurate tool diagnosing SIBO. We aim to analyze whether a lactulose nutrient challenge test (NCT), previously shown to separate DGBI from healthy volunteers, is equivalent to ScLHBT in diagnosing SIBO. Methods We studied data of 81 DGBI patients undergoing ScLHBT with 30 g lactulose and 300 mL water as well as NCT with 30 g lactulose and a 400 mL liquid test meal. Differences in proportion of positive SIBO diagnoses according to specified cecal load and time criteria for NCT and ScLHBT, respectively, were tested in an equivalence trial. An odds ratio (OR) range of 0.80-1.25 was considered equivalent. Results Diagnosis of SIBO during NCT was not equivalent to SIBO diagnosis in ScLHBT, considering a hydrogen increase before cecal load of 5.0%, 7.5%, or 10.0%, respectively ([OR, 3.76; 90% CI, 1.99-7.09], [OR, 1.87; 90% CI, 1.06-3.27], and [OR, 1.11; 90% CI, 0.65- 1.89]). Considering only time to hydrogen increase as criterion, the odds of a positive SIBO diagnosis in the NCT (0.65) was lower than in ScLHBT (1.70) (OR, 0.38; 90% CI, 0.23-0.65). Conclusions This study could not show an equivalence of NCT and ScLHBT in diagnosing SIBO. A possible explanation might be the different transit times owing to unequal testing substances. The effect of this deviation in relation to consecutive therapy regimens should be tested in further prospective studies.

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Original Article

Nutrient Challenge Testing Is Not Equivalent to Scintigraphy–Lactulose Hydrogen Breath Testing in Diagnosing Small Intestinal Bacterial Overgrowth

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Background/Aims
Small intestinal bacterial overgrowth (SIBO) is a common condition in disorders of gut-brain interaction (DGBI). Recently, a combined scintigraphy–lactulose hydrogen breath test (ScLHBT) was described as an accurate tool diagnosing SIBO. We aim to analyze whether a lactulose nutrient challenge test (NCT), previously shown to separate DGBI from healthy volunteers, is equivalent to ScLHBT in diagnosing SIBO.

Methods
We studied data of 81 DGBI patients undergoing ScLHBT with 30 g lactulose and 300 mL water as well as NCT with 30 g lactulose and a 400 mL liquid test meal. Differences in proportion of positive SIBO diagnoses according to specified cecal load and time criteria for NCT and ScLHBT, respectively, were tested in an equivalence trial. An odds ratio (OR) range of 0.80-1.25 was considered equivalent.

Results
Diagnosis of SIBO during NCT was not equivalent to SIBO diagnosis in ScLHBT, considering a hydrogen increase before cecal load of 5.0%, 7.5%, or 10.0%, respectively ([OR, 3.76; 90% CI, 1.99-7.09], [OR, 1.87; 90% CI, 1.06-3.27], and [OR, 1.11; 90% CI, 0.65-1.89]). Considering only time to hydrogen increase as criterion, the odds of a positive SIBO diagnosis in the NCT (0.65) was lower than in ScLHBT (1.70) (OR, 0.38; 90% CI, 0.23-0.65).

Conclusions
This study could not show an equivalence of NCT and ScLHBT in diagnosing SIBO. A possible explanation might be the different transit times owing to unequal testing substances. The effect of this deviation in relation to consecutive therapy regimens should be tested in further prospective studies.
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Key Words
Breath test; Hydrogen; Lactulose; Nutrients; Radionuclide imaging

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Introduction

Hydrogen based breath tests have been employed for a substantial time using a myriad of substances and protocols. However, if done correctly, they are a useful, safe and cost-effective diagnostic adjunct in the evaluation of gastrointestinal problems.[1] Particularly in small intestinal bacterial overgrowth (SIBO), lactulose and glucose breath tests represent widely used non-invasive alternatives to other SIBO diagnostics.[1,2] In disorders of gut-brain interaction (DGBI), SIBO is a frequently mentioned condition, with a reported prevalence of 38-54% in patients with irritable bowel syndrome (IBS) tested by lactulose hydrogen breath test (LHBT).[3,4] Accordingly, a significant improvement of abdominal symptoms was shown in response to antibiotic treatment in an IBS cohort with high SIBO prevalence.[5] This finding was underlined by 2 identically designed, phase 3, double-blinded placebo-controlled trials with a non-absorbable antibiotic in non-constipated IBS patients.[6] However, this study did not focus on the mechanism of effect and the bacterial eradication was not based on a prior SIBO diagnosis. Even though standardization of SIBO diagnostics has been proposed, there is still significant heterogeneity in how the test is performed. By many researchers, aspiration of small bowel fluid, culturing and quantification of bacteria is regarded gold standard for diagnosing SIBO.[7] However, this procedure is time-consuming, expensive, invasive, and limited to the proximal small bowel,[1] thereby missing SIBO in the distal part of the small bowel. A study by Zhao et al[8] introduced combined scintigraphy–LHBT (ScLHBT) as an accurate and reproducible diagnostic test for SIBO. Scintigraphy involves radiation exposure, a dedicated infrastructure, and is very expensive. The cost of LHBTs depends on local reimbursement but is in the range of 10-20% of scintigraphies. While different studies investigated LHBT in diagnosing SIBO, there is no published data in the use of nutrient challenge tests (NCT), consisting of a standardized liquid test meal in combination with a standard LHBT.[9] However, performing a NCT, originally developed to discriminate IBS patients from healthy volunteers, was recently shown to be useful in discriminating healthy volunteers from subjects with functional dyspepsia (FD), potentially expanding its range of applications.[9-11] In this study we aim to analyze whether the NCT, as a cost-effective and radiation-free alternative to scintigraphy, is equivalent to the ScLHBT in diagnosing SIBO.

Materials and Methods

In this retrospective study data of 81 consecutive DGBI patients treated at our academic tertiary gastrointestinal center with signed informed consent to the use of their health-related data for scientific purposes were analyzed. Inclusion criteria were age (older than 18 years) and complete testings for SIBO by NCT as well as ScLHBT between July 2014 and April 2018. All patients underwent both tests. ScLHBT to test for SIBO and NCT in the clinical setting primarily to test for food/fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) intolerance and secondarily (the not yet proven) SIBO diagnostic analyzed in this study. The study was approved by the local ethical committee (BASEC number 2016-01931).

Nutrient Challenge Test

For the NCT, patients consumed 30 g lactulose combined with 400 mL Ensure (600 kcal, 20 g fat, 81 g carbohydrates, and 25 g protein) after overnight fasting. Every 10 minutes and for a total duration of 180 minutes, hydrogen breath levels were measured and 5 abdominal symptoms (bloating, pain, bowel sounds, diarrhea, and nausea) were recorded using a 5-point Likert-like scale. Hydrogen levels were measured by Breathalyzer-HydroCheck (NEOMED System, Adelhausen, Germany). During NCT SIBO was diagnosed if hydrogen levels increased by more than 10 parts per million (ppm) in 2 consecutive measurements compared to baseline within 20-90 minutes after ingestion. Patients with no hydrogen increase or not higher than 10 ppm for 180 minutes were considered "hydrogen non-producers."

Combined Scintigraphy With Lactulose Hydrogen Breath Test

For the ScLHBT, patients consumed 30 g lactulose in 300 mL water after overnight fasting. Different criteria for abnormal LHBT and ScLHBTs are used to date. Previous findings demonstrated 5% cecal load (CL)[8,12,13] as well as 10% CL[14,15] to be useful markers of abnormal ScLHBT. We therefore tested different criteria to diagnose SIBO. The first 3 criteria were based on the CL: SIBO was diagnosed if hydrogen increased more than 10 ppm in 2 consecutive measurements compared to baseline before the detection of 5.0%, 7.5%, or 10.0% cecal activity (^{99m}technetium diethylene-triamine-pentaacetate (^{99m}Tc-DTPA) in scintigraphy. All scintigraphic measurements were analyzed by an experienced specialist in nuclear medicine. As a fourth criterion, hydrogen increase

by more than 10 ppm in 2 consecutive measurements compared to baseline within 20-90 minutes after ingestion, was used (comparable to the NCT analysis). Hydrogen levels were measured by Breathalyzer-HydroCheck (NEOMED System). Statistical analyses were performed for all 4 SIBO ScLHBT criteria and compared to SIBO proportions in NCT. Patients with no hydrogen increase or not higher than 10 ppm for 180 minutes were considered "hydrogen non-producers."

In a subgroup analysis we analyzed data of ScLHBT only to check for equivalence of the different diagnostic criteria used in ScLHBT: we tested for equivalence of a clinically significant hydrogen increase by 90 minutes as compared to the hydrogen increase by scintigraphy-controlled CL as well as for equivalence of abdominal symptom generation.

Disorders of Gut-Brain Interaction

Diagnosis of DGBI and DGBI subcategories IBS, IBS-FD overlap, FD, and functional abdominal pain or bloating (FAPB) were defined according to Rome III and IV criteria.[16,17]

Statistical Methods

A sample size calculation for equivalence testing in proportions according to Chow and Shao[18] indicated that at least 78 patients in each group would be needed to demonstrate an equivalence of SIBO proportions diagnosed in NCT compared to ScLHBT with an 80% power and an alpha of 0.05. To visualize distribution of absolute hydrogen values and hydrogen differences, normal quantile-quantile plots were used. Two different statistical methods were used to analyze equivalence of SIBO diagnostics: on the one hand odds ratio (OR) and on the other hand analysis of data from matched samples with dichotomous outcome according to Fleiss et al[19] were used to assess whether NCT is equivalent to ScLHBT in diagnosing SIBO. An OR range between 0.80 and 1.25 was considered equivalent.[20] Conversion to equivalence margin in analysis of data from matched samples with dichotomous outcome resulted in a ΔP of $\pm$ 0.05 (for detailed calculations see Supplementary Table). Hence, the equivalence margin for matched samples analyses was set at $\pm$ 0.05. For continuous variables, median and range were used for non-normally distributed data. To compare this data, Wilcoxon rank sum tests were used. For categorical data, chi-squared and Fisher's exact test were used. Statistical analyses were performed with R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

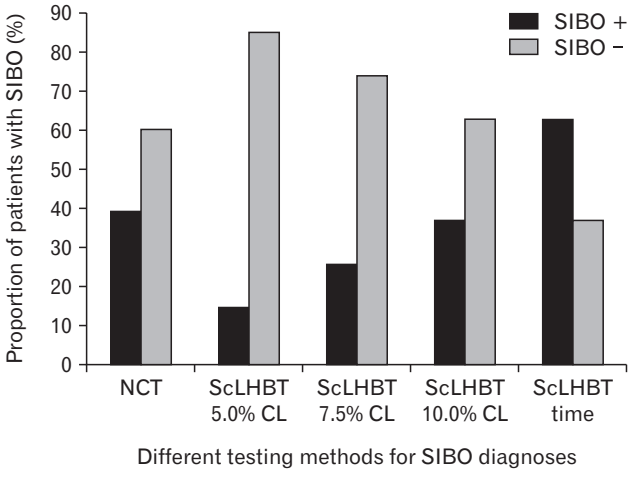

Figure 1. Proportions of positive small intestine bacterial overgrowth (SIBO) diagnosis. NCT: SIBO diagnosis in nutrient challenge test. Combined scintigraphy lactulose hydrogen breath test (ScLHBT) 5.0% cecal load (CL), 7.5% CL, and 10.0% CL: SIBO positive if more than 10 ppm hydrogen increase from baseline in at least 2 consecutive measurements before detected CL of 5.0%, 7.5%, and 10.0%. ScLHBT time: SIBO positive if more than 10 ppm hydrogen increase from baseline in at least 2 consecutive measurements by 90 minutes after ingestion of testing substance.

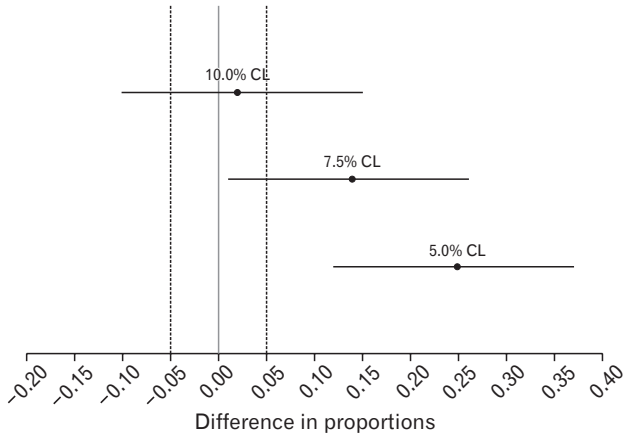

Figure 2. Equivalence testing of small intestine bacterial overgrowth (SIBO) diagnosis in nutrient challenge test (NCT) and different criteria in combined scintigraphy lactulose hydrogen breath test, according to Fleiss et al.[19] SIBO was diagnosed if hydrogen increased more than 10 parts per million (ppm) in 2 consecutive measurements compared to baseline before the detection of 5.0% (5.0% cecal load [CL]), 7.5% (7.5% CL), or 10.0% (10.0% CL) cecal activity in scintigraphy. During NCT SIBO was diagnosed if hydrogen levels increased by more than 10 ppm in 2 consecutive measurements compared to baseline within 20-90 minutes after ingestion. Horizontal lines representing 90% confidence interval (CI). Vertical dotted lines representing upper (0.05) and lower (–0.05) equivalence limit. Equivalence is given if 90% CI (horizontal line) does not exceed any of the equivalence margins (vertical dotted lines). CL, cecal load.

Results

Eighty-one patients were included in the analysis (men, 18/81 [22.2%]; median age, 39 years [range 19-70 years]). The median body weight was 60 kg (range, 43-102 kg). All patients suffered from DGBI. IBS was the most prevalent subtype (n = 33, 40.7%), followed by IBS-FD overlap (n = 30, 37.0%), FD (n = 9, 11.1%), and FAPB (n = 9, 11.1%). Of all IBS patients 13 were diagnosed with IBS with constipation, 10 with IBS with diarrhea, 7 with IBS mixed type, and 3 with unclassified IBS.

Small Intestinal Bacterial Overgrowth Diagnoses

Small intestinal bacterial overgrowth diagnosis by time criterion

SIBO was diagnosed in 32/81 (39.5%) patients with NCT and 51/81 (63.0%) patients with ScLHBT using SIBO diagnostic criteria of more than 10 ppm hydrogen increase as compared to baseline within 20-90 minutes after the intake of the testing substance. Difference in proportions was −0.23 (90% CI, −0.34-−0.12], failing to show equivalence between the 2 tests since the 90% CI exceeds equivalence margins of ± 0.05

Small intestinal bacterial overgrowth diagnosis by cecal load 5.0% criterion

Based on 5.0% CL measurement in ScLHBT, 32/81 subjects (39.5%) were diagnosed with SIBO by ScLHBT, in contrast only 12/81 (14.8%) subjects were tested positive with NCT in the same subgroup. Difference in proportions was 0.25 (90% CI, 0.12-0.37). No equivalence was shown (Fig. 1 and 2).

Small intestinal bacterial overgrowth diagnosis by cecal load 7.5% criterion

Based on the criterion of 7.5% CL in ScLHBT, SIBO was diagnosed in 21/81 (25.9%) subjects with NCT and in 32/81 subjects (39.5%) with ScLHBT, resulting in a difference of proportions of 0.14 (90% CI, 0.01-0.26). No equivalence was shown (Fig. 1 and 2).

SIBO diagnosis by cecal load 10.0% criterion

Based on the 10.0% CL measurements, 30/81 patients (37.0%) were diagnosed with SIBO with NCT and 32/81 (39.5%) with ScLHBT. Difference of proportions was 0.02 (90% CI, −0.10-

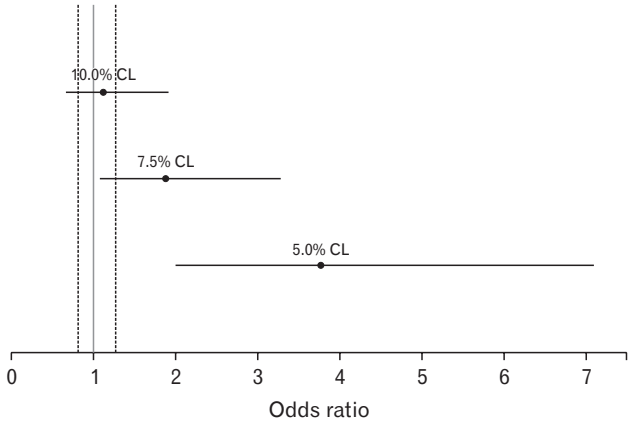

Figure 3. Equivalence plot of odds ratio (OR) in small intestine bacterial overgrowth (SIBO) findings in nutrient challenge test (NCT) and different criteria of combined scintigraphy lactulose hydrogen breath test. SIBO was diagnosed if hydrogen increased more than 10 parts per million (ppm) in 2 consecutive measurements compared to baseline before the detection of 5.0% (cecal load [CL] 5.0%), 7.5% (CL 7.5%), or 10.0% (CL 10.0%) cecal activity in scintigraphy. During NCT SIBO was diagnosed if hydrogen levels increased by more than 10 ppm in 2 consecutive measurements compared to baseline within 20-90 minutes after ingestion. Horizontal lines representing 90% confidence interval (CI). Vertical dotted lines representing upper (1.25) and lower (0.80) equivalence limit. Equivalence is given if 90% CI (horizontal line) does not exceed any of the equivalence margins (vertical dotted lines). CL, cecal load.

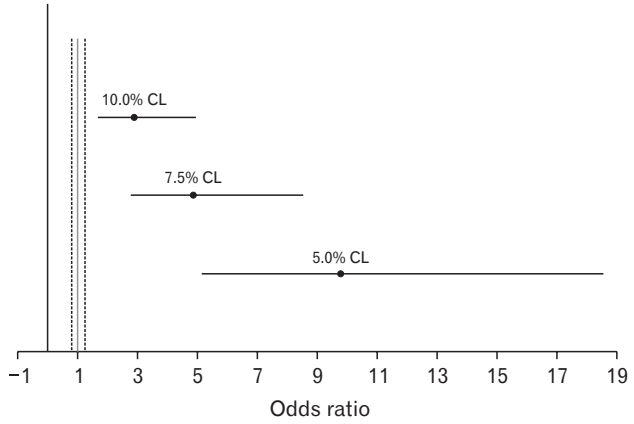

Figure 4. Equivalence plot of odds ratio (OR) in small intestine bacterial overgrowth findings in combined scintigraphy lactulose hydrogen breath test (ScLHBT) by time criterion and different cecal load (CL) criteria. Time criterion (hydrogen increase > 10 ppm in at least 2 consecutive measurements by 90 minutes) in ScLHBT vs 10 ppm hydrogen increase from baseline in at least 2 consecutive measurements before detected CL of 5.0%, 7.5%, and 10.0%). Horizontal lines representing 90% confidence interval (CI). Vertical dotted lines representing upper (1.25) and lower (0.80) equivalence limit. Equivalence is given if 90% CI (horizontal line) does not exceed any of the equivalence margins (vertical dotted lines).

0.15). No equivalence was shown (Fig. 1 and 2).

Odds Ratio

Time criterion

The odds of positive SIBO testing in NCT (0.65) was lower than in ScLHBT (1.70) based on time criteria (OR, 0.38; 90% CI, 0.23-0.65), therefore failing to confirm equivalence.

Cecal load 5.0% criterion

The odds of positive SIBO testing by CL 5.0% criterion was higher in NCT (0.65) than in ScLHBT (0.17) (OR, 3.76; 90% CI, (1.99-7.09). Equivalence was not confirmed (Fig. 3).

Cecal load 7.5% criterion

In the 7.5% CL measurements, odds of positive SIBO result was higher in NCT (0.65) than in ScLHBT (0.35) (OR, 1.87; 90% CI, 1.06-3.27). Equivalence was not shown (Fig. 3).

Cecal load 10.0% criterion

In the 10.0% CL measurements, the odds of positive SIBO testing was higher in NCT (0.65) than in ScLHBT (0.59) (OR, 1.11; 90% CI, 0.65-1.89). Equivalence was not shown (Fig. 3).

Subanalysis: Significant Hydrogen Increase

The first hydrogen increase > 10 ppm in at least 2 consecutive measures occurred at a median of 50 minutes (range 20-170 minutes) in NCT and at 70 minutes (range 20-160 minutes) in ScLHBT. Median CL at clinically significant hydrogen increase in ScLHBT was 9.0% (range 0.0-16.0%). In NCT, a total of 35 patients (43.2%) were hydrogen non-producers while there were only 20 hydrogen non-producers (24.7%) in ScLHBT.

Subanalysis: Significant Symptom Increase

The first clinically significant median increase (= increase of at least 1 point on Likert scale in 2 consecutive measurements) of bloating occurred at 30 minutes (20-170 minutes) with NCT, and at 40 minutes (20-140 minutes) with ScLHBT ($P = 0.535$). Abdominal pain significantly increased at 30 minutes (20-180 minutes) with NCT, and at 50 minutes (20-160 minutes) with ScLHBT ($P = 0.078$). Clinically significant nausea occurred after a median observation time of 20 minutes (20-120 minutes) and 30 minutes (20-180 minutes) ($P = 0.007$), borborygmi at 30 minutes (20-170 minutes) and 40 minutes (20-180 minutes) ($P = 0.048$), and diarrhea at 80 minutes (20-180 minutes) and 80 minutes (20-170 minutes) ($P = 0.119$) in NCT and ScLHBT, respectively.

Subanalysis: Scintigraphy–Lactulose Hydrogen Breath Test Only

Analyzing the results within ScLHBT itself was superior to the prevalence of SIBO by time criterion as compared to scintigraphy-controlled analysis (Fig. 1 and 4).

Discussion

This study did not confirm an equivalence in diagnosing SIBO by NCT as compared to ScLHBT. While NCT was proven to be a good non-invasive test to discriminate IBS and FD patients from healthy volunteers,[11] its role in diagnosing SIBO is not established yet. One reason for the non-equivalence of NCT and ScLHBT may be based on the 2 different testing substances entailing different orocecal transit times (OCTT). This difference may be caused by the delayed gastric emptying after addition of a liquid test meal in NCT on the one hand, in contrast to an increased small bowel transit time due to the application of lactulose only on the other hand.[15] An additional cause for lower rates of SIBO by ScLHBT (based on CL) might be the slight delay of hydrogen increase as compared to imaging of CL. Bond et al[13] showed a 5-8 minute delay in hydrogen increase due to fermentation time of lactulose, hydrogen absorption to the blood, and final pulmonary excretion of hydrogen. The later hydrogen increase was also confirmed by Yu et al.[12] They found that in 22 out of 25 (88.0%) IBS patients the hydrogen increase occurred later than the ^{99m}Tc reached the cecum. However, in contrast to our study, they considered a hydrogen increase of > 20 ppm as clinically significant. Read et al[21] could demonstrate that (0.5 g and 5 g boluses of) lactulose infused directly into the colon resulted in a significant hydrogen increase of 5-10 ppm within a few minutes. According to this and in line with the study of Esposito et al,[22] we used 10 ppm (in 2 consecutive measurements) by 90 minutes as a marker of abnormal LHBT/ScLHBT in order to increase sensitivity and decrease false negative SIBO results.

To date, a broad range of diagnostic criteria for abnormal LHBT and ScLHBTs are used. Previous findings demonstrated 5.0% CL accumulation[8,12,13] and 10.0% accumulation[14,15] to be useful markers of abnormal ScLHBT. We therefore analyzed data for 5.0%, 10.0%, as well as 7.5% cecal load, showing the largest discrepancy of equivalent SIBO proportions at 5.0%, followed by 7.5% and 10.0%. This is also in line with the hypothesis of the slower OCTT in the NCT containing the liquid test meal.

However, in this study there are some limitations: We found a

high prevalence of hydrogen non-producers. In NCT, the prevalence of hydrogen non-producers was as high as 43.0%, compared to 25.0% in ScLHBT. This fact complicates the interpretation of SIBO diagnostics. Although this comparably high number of hydrogen non-producers is in line with reports from earlier studies,[23,24] it is a limitation of our study cohort with regard to equivalence testing. A second limitation might be the heterogenous patient cohort including IBS as well as FD and functional abdominal pain and bloating patients. However, we do assume that this did not substantially influence our results since the 2 tests were performed in the same patient cohort. Additionally, a majority of our study subjects suffered from IBS or IBS-FD overlap, the most frequently investigated DGBI diagnoses in SIBO studies.[6,25,26] However, the association and impact of SIBO in DGBI patients remains controversial. While a significant reduction of global IBS symptoms could be shown after therapy with Rifaximin in a previous study,[6] no preselection of SIBO diagnosis was performed there. A preceding study could though show a normalization of a LHBT after antibiotic therapy in IBS patients.[27] They used a hydrogen increase before 90 minutes and secondary, the originally traditional but not well validated 2 peaks as diagnostic criteria, which both were used for SIBO diagnostics by other studies. Despite these studies showing significant impact of antibiotic therapies on abdominal burdens in DGBI patients, the direct association between SIBO and DGBI is not clear, as there may be different effect mechanism: by affecting gut bacteria gas production might be reduced and therefore directly decrease symptoms or indirectly reduce immune response or both. However, whether it is directly linked to SIBO, including its controversially discussed testing methods, is not yet confirmed. The additional fact that in our study we analyzed SIBO itself in association with a not clearly validated diagnostic gold standard, but though as compared to ScLHBT, which represents an accurate test for SIBO diagnostics, may represent a limitation. In a subanalysis of SIBO diagnosis according to hydrogen increase by 90 minutes as compared to scintigraphic criteria, we could not confirm equivalence either. This finding is in line with the findings of Yu et al,[12] who demonstrated a discordance of positive LHBT and ScLHBT results. They even argued that abnormal LHBT tests rather represent OCTT than SIBO. However, a few years later in the North American Consensus, based on a pooled positivity rate of LHBT or glucose breath test including 19 studies with a total of 888 study subjects, LHBT was regarded as a valuable non-invasive alternative for diagnosing SIBO.

In contrast to our study, most of the studies used LHBT without an additional test meal. However, to better represent physiological conditions and because the NCT was shown useful to discriminate IBS and FD patients from healthy volunteers,[9-11] we used the NCT. The test meal might also explain the significant differences in the occurrence of nausea and borborygmi. Farré et al[28] demonstrated that in FD patients particularly postprandial distension thresholds are associated with the severity of meal-related symptom generation. Additionally, increased visceral sensitivity was shown in FD and IBS patients after nutrient infusion.[29-31] In our study, besides a significant difference in nausea and borborygmi, abdominal pain tended to occur earlier in NCT too. We attribute this to the visceral hypersensitivity in particular to nutrients and volume distension in an additional test meal (NCT), as compared to lactulose only (ScLHBT) in DGBI patients. With regard to diarrhea, no significant difference was seen, which is probably due to the low overall prevalence of diarrhea in our cohort. However, the earlier symptom generation in NCT in contrast to the later hydrogen increase leads to the assumption that rather the substance of consumption (test meal and lactulose vs lactulose only) than the hydrogen increase or SIBO diagnosis alone influences symptom generation in DGBI patients.

In addition to the different abdominal symptom generation, the main hypothesis of an equivalent proportion of SIBO diagnosis in NCT as compared to ScLHBT could not be confirmed. This leads us to the assumption that the less expensive and radiation-free NCTs cannot replace ScLHBT, independent of the criteria used for diagnosing SIBO. Whether and to what extent this influences SIBO therapies, in particular antibiotic therapies, in FIGD patients remains unclear. Further prospective and multicenter studies based on therapies and outcomes according to NCT as compared to ScLHBT test results are desirable.

Supplementary Material

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm19162.

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Conflicts of interest: None.

Author contributions: Valeria Schindler wrote the article, designed the study, collected data, and statistically analyzed data;

Martin Hüllner collected and processed data and revised the manuscript; Fritz Murray collected data and revised the manuscript; Anton S Becker analyzed data and revised the manuscript; Larissa Schnurre collected data and revised the manuscript; Valentine Bordier collected data and revised the manuscript; and Daniel Pohl designed the study, analyzed data and edited the manuscript. All authors have read and approved the final manuscript.

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